PATENT SPECIFICATION

NO DRAWINGS

Inventors: BERNARD GEORGE BOGGIANO, GEOFFREY BALDWIN JACKMAN, VLADIMIR PETROW and OLIVER STEPHENSON

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COMPLETE SPECIFICATION

Improvements in or relating to the Manufacture of N-Mono-Substituted Piperazines

We, THE BRITISH DRUG HOUSES LIMITED, a British Company, of 16—34, Graham Street, City Road, London, N.1, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is for improvements in or relating to organic compounds and has particular reference to a new process for the manufacture of N-monosubstituted piperazines.

It is an object of the present invention to provide a new process for the manufacture of a wide range of N-monosubstituted piperazines as hereinafter defined, which process gives yields which are often substantially higher than those obtained by the employment of methods hitherto known to those skilled in the art.

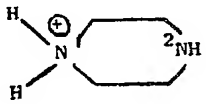
N-Monosubstituted piperazines are essential intermediates in the manufacture of piperazine derivatives employed in medicine for example as antihistaminics, travel-sickness remedies and anthelmintics.

The manufacture of the N-monosubstituted derivatives of piperazine is complicated by the fact that there are present in piperazine having the formula

(I)

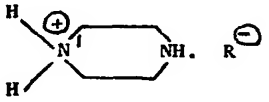
two basic centres N^1 and N^2 of equal reactivity towards alkylating agents, so that monoalkylation without simultaneous dialkylation is difficult to achieve. Thus monoalkylation of piperazine by methods hitherto known to those skilled in the art generally gives mixtures containing the unchanged base, the N^1-monosubstituted derivative and significant quantities of the N^1N^2-disubstituted derivative, which mixtures are generally difficult to separate so that there is considerable loss in yield of N^1-monosubstituted derivative. In addition the unwanted production of significant quantities of the N^1N^2-disubstituted derivative is wasteful.

We have made the discovery that, in contrast to piperazine itself, the two reactive centres N^1 and N^2 present in the monopiperazinium ion (II)



(II)

derived from the corresponding monopiperazinium salt (III)



(III)

where R is an anionic radical derived from an acid as hereinafter defined, are no longer equal in reactivity towards alkylating agents, and that alkylation of salts containing such monopiperazinium ions gives excellent yields of N-monosubstituted piperazines substantially free from N^1N^2-disubstituted derivatives. This is a discovery of industrial importance as it opens the way to the economic production of a wide range of N-monosubstituted derivatives of piperazine in excellent yields and by a substantially one-stage process.

According to the present invention there is provided a process for the manufacture of an N-monosubstituted piperazine which process comprises reacting in the presence of an organic or aqueous organic solvent an alkylating agent containing up to 6 carbon atoms or an aralkylating agent with a monopiperazinium salt derived from an acid with dissociation constant lying below the second acid dissociation constant of the piperazine in the solvent system employed for the condensation.

The monopiperazinium salt is prepared by reacting piperazine or its hexahydrate in an organic or aqueous organic solvent with the appropriate quantity of acid. The monopiperazinium salt will separate from solution or remain in the solution from which it may be recovered by removal of the solvent. It is, however, convenient to employ the monopiperazinium salts *in situ* without prior isolation, the amount of acid added being as nearly as possible the quantity necessary to convert the piperazine to the monopiperazinium salt.

The alkylating agent may be methyl or ethyl sulphate or an alkyl halide, in particular an alkyl bromide or iodide, but not an alkyl fluoride.

The alkylating or aralkylating agent may have two reactive centres; thus it may be an aliphatic or araliphatic $\alpha\omega$-dichloride, dibromide or diiodide, in particular, the alkylating agent may be an $\alpha.\omega$-dibromide or diiodide containing up to 6 carbon atoms.

The aralkylating agent may be a chloride, bromide or iodide of the type

$$\mathrm{Hal}.(CH_2)_nAr,$$

where n is not greater than 6 and Ar is an aromatic nucleus and in particular a phenyl, naphthyl or diphenyl nucleus, which may be additionally substituted by alkyl, alkoxy, halogen or nitro groups.

The invention is applied to monopiperazinium salts derived from acids as herein defined providing the corresponding monopiperazinium salts are soluble in the solvents employed for the condensations at the temperatures at which the condensations are performed, do not react with the solvents employed for the condensations, and do not decompose under the experimental conditions employed for the condensations.

The invention is applied to monopiperazinium salts derived from acids with dissociation constants lying below the second acid dissociation constant of the piperazine in the solvent system employed for the condensation. Thus when piperazine is employed in aqueous ethanolic solution the monopiperazinium salt may be derived from acids with dissociation constants lying below the second acid dissociation constant of piperazine (pKa_2 =9.66 in water at 25° C.). Acids which satisfy this condition and thus fall within the scope of the invention are exemplified by:

acetic acid,
succinic acid,
citric acid,
benzoic acid,
toluene-*p*-sulphonic acid,
hydrochloric and hydrobromic acids, and
sulphuric acid.

Hydrochloric acid is the preferred acid.

The invention may be performed in a variety of solvent systems including such organic solvents as dioxan, ethoxy-ethanol and alkanols containing up to 5 carbon atoms, with or without the addition of water. Aqueous ethanol is the preferred solvent system.

The invention may be performed by adding the appropriate proportion of alkylating or aralkylating agent to a solution of the monopiperazinium salt in the appropriate solvent. Heating the mixture may be necessary with alkylating agents of low reactivity.

In carrying out the process of the invention economically, it is clearly necessary to adjust the relative proportions of alkylating or aralkylating agent and monopiperazinium salt in such a way as to obtain as high a yield of product as possible without employment of too great an excess of monopiperazinium salt. It will be obvious to those skilled in the art that the proportion of monopiperazinium salt employed should not be less than one molar proportion relative to each alkylating unit. At the same time it is economically inadvisable to employ substantially more than 2.1 molar proportions of monopiperazinium salt to each alkylating unit. With monopiperazinium salts derived from hydrochloric acid and other strong mineral acids, yields of monosubstitution product approaching the optimum yield are obtained by employing 1.9 to 2.1 molar proportions of monopiperazinium salt to each alkylating unit. With weak organic acids it is possible to use a smaller proportion of monopiperazinium salt with only moderate drop in yield of N-monosubstitution product, but the proportion of monopiperazinium salt employed should not be less than one molar proportion to each alkylating unit otherwise the process becomes uneconomical.

Following is a description by way of example of methods of carrying the invention into effect.

EXAMPLE 1.

N-*m*-Methylbenzylpiperazine

A solution of monopiperazinium chloride (24.5 g., 0.2 mole) in a mixture of ethanol (100 ml.) and water (35 ml.) was cooled to 20° C. and *m*-methylbenzylbromide (18.5 gm., 0.1 mole) added with stirring. Stirring was continued for one hour at 20° C. and then for 30 minutes at 70° C., when the eth-

anol was removed at reduced pressure. The residue was made basic by the addition of a slight excess of 5N sodium hydroxide. The oil which separated was removed and the aqueous layer extracted with benzene. The benzene extract was combined with the oil and the benzene distilled off. Distillation of the residue at 0.2 mm. yielded N-*m*-methylbenzylpiperazine as an oil, b.p. 100° to 105° C.

EXAMPLE 2.

A solution of monopiperazinium chloride was prepared *in situ* in aqueous methyl alcohol by adding hydrochloric acid (17.5 ml. of 11.4N, 0.2 mole) to a solution of piperazine hexahydrate (38.8 g., 0.2 mole) in methanol (100 ml.). The solution was cooled to 20° C. and *m*-methylbenzylbromide (18.5 gm., 0.1 mole) added with stirring. Stirring was continued for 30 minutes at 70° C. N-*m*-Methylbenzylpiperazine was isolated exactly as described in Example 1, as an oil, b.p. 123° to 127° C., at 1.5 mm.

EXAMPLE 3.

The reaction described in Example 2 was carried out in exactly the same way except that *iso*propanol (100 ml.) was used in place of methanol. The N-*m*-methylbenzylpiperazine was obtained as an oil, b.p. 122° to 126° C., at 1.5 mm.

EXAMPLE 4.

The reaction carried out in Example 2 was repeated using β-ethoxyethanol (100 ml.) in place of methanol. The mixture was stirred vigorously throughout because of the tendency to form two layers. The N-*m*-methylbenzylpiperazine isolated in the normal manner, had b.p. 122° to 124° C. at 1.5 mm.

EXAMPLE 5.

A solution of monopiperazinium bromide was prepared *in situ* in aqueous ethanol by adding 47% hydrobromic acid (34.5 g., 0.2 mole) to a solution of piperazine hexahydrate (38.8 g., 0.2 mole) in ethanol (80 ml.). The solution was heated to 70° C. and *m*-methylbenzylbromide (18.5 g., 0.1 mole) added slowly. Stirring was continued at 70° C., for 30 minutes. Isolation of the N-*m*-methylbenzylpiperazine as described in Example 1 yielded an oil, b.p. 100° to 102° C. at 0.2 mm.

EXAMPLE 6.

A solution of monopiperazinium acetate was prepared *in situ* in aqueous ethanol by adding glacial acetic acid (6.0 g., 0.1 mole) to a solution of piperazine hexahydrate (19.4 gm., 0.1 mole) in a mixture of ethanol (100 ml.) and water (20 ml.). The solution was heated to 70° C. and *m*-methylbenzylbromide (18.5 g., 0.1 mole) was added slowly with stirring. Stirring was continued at 70° C. for 30 minutes. N-*m*-methylbenzylpiperazine, isolated in the manner described in previous examples, had b.p. 123° to 125° C., at 1.5 mm.

EXAMPLE 7.

A suspension of monopiperazinium sulphate was prepared *in situ* in aqueous ethanol by adding 98% sulphuric acid (5.3 ml. of 37.5 N, 0.1 mole) to a solution of piperazine hexahydrate (38.8 g., 0.2 mole) in a mixture of ethanol (100 ml.) and water (15 ml.). By heating to 70° C. a solution was formed; *m*-methylbenzylbromide (18.5 g., 0.1 mole) was then added slowly and the stirring continued at 70° C. for 30 minutes. The N-*m*-methylbenzylpiperazine was isolated exactly as described in Example 1, as an oil, b.p. 103° to 105° C., at 0.2 mm.

EXAMPLE 8.

N-Methylpiperazine

A solution of monopiperaziniumchloride in aqueous ethanol was prepared *in situ* by adding slowly concentrated hydrochloric acid (173 ml., 2 moles) to a solution of piperazine hexahydrate (388 g., 2 moles) in ethanol (800 ml.) in a 3-neck round-bottomed flask fitted with stirrer, condenser and dropping-funnel. The mixture was cooled to room temperature, stirred and methyl iodide (142 g., 1 mole) added slowly. After the addition was complete, stirring was continued for 90 minutes at room temperature and then for 2 hours at 70° C. The mixture was cooled, treated with concentrated hydrochloric acid (86.5 ml. of 11.6 N, 1 mole), concentrated to half bulk and the insoluble piperazine *bis* hydrochloride filtered off. The filtrate was evaporated to dryness at reduced pressure, dissolved in methanol (1 litre) and filtered to remove a little more of the insoluble piperazine *bis* hydrochloride. The filtrate was treated with a concentrated solution of sodium methoxide (108 g., 2 mole), filtered to remove sodium chloride and distilled through an efficient fractionating column. After removal of methanol and a small fore-run, N-methylpiperazine was obtained, b.p. 134° to 136° C.

EXAMPLE 9.

N-*n*-Amylpiperazine

A solution of monopiperazinium chloride was prepared *in situ* in aqueous ethanol by adding concentrated hydrochloric acid (17.5 ml of 11.4 N, 0.2 mole) to a stirred solution of piperazine hexahydrate (38.8 gm.) in ethanol (180 ml.). The mixture was cooled to 20° C. and *n*-amylbromide (15.1 g., 0.1 mole) added slowly. After the addition was completed, stirring was continued for 1 hour at room temperature and for 30 minutes at 70° C. The N-*n*-amylpiperazine, isolated in the normal manner, had b.p. 110° to 114° C. at about 30 mm.

EXAMPLE 10.

N-*o*-Methylbenzylpiperazine

A solution of monopiperazinium chloride was prepared *in situ* in aqueous ethanol by adding concentrated hydrochloric acid (17.3 ml. of (11.5 N, 0.2 mole) to a stirred solu-

tion of piperazine hexahydrate (38.8 gm., 0.2 mole) in ethanol (80 ml.). The mixture was cooled to 20° C. and *o*-methylbenzylbromide (18.5 gm., 0.1 mole) added slowly dropwise. After the addition was complete, the mixture was stirred for 2 hours at room temperature and for 30 minutes at 70° C. The N-*o*-methylbenzylpiperazine, isolated as described in earlier examples, had b.p. 104° to 106° C. at 0.05 mm.

EXAMPLE 11.

N-*m*-Methylbenzyl piperazine

A solution of monopiperazinium toluene *p*-sulphonate was prepared *in situ* from piperazine hexahydrate (38.8 g.) and toluene *p*-sulphonic acid monohydrate (38 g.) in ethanol (80 ml.). The solution was cooled to 20° C. and *m*-methylbenzyl bromide (18.5 g.) added with stirring. Stirring was continued for 1 hour at room temperature and for 30 minutes at 70° C. The *product* isolated as described in Example 1 had b.p. 130° to 132° C. at 1.4 mm.

EXAMPLE 12.

A solution of monopiperazinium benzoate was prepared *in situ* from piperazine hexahydrate (38.8 g.) and benzoic acid (24.4 g.) in ethanol (80 ml.). This solution was reacted with m-methylbenzyl bromide (18.5 g.) exactly as described in Example 11. The *product*, isolated as above had b.p. 110° to 116° C. at 0.6 mm.

EXAMPLE 13.

A solution of monopiperazinium citrate was prepared *in situ* by dissolving piperazine hexahydrate (29.1 g.) and citric acid monohydrate (10.5 g.) in ethanol (60 ml.), and reacted as described in previous examples with *m*-methylbenzyl bromide (18.5 g.). The *product* isolated in the usual manner, had b.p. 110° to 114° C. at 0.5 mm.

EXAMPLE 14.

N-*p*-Methoxybenzyl piperazine

A solution of monopiperazinium chloride was prepared *in situ* by adding concentrated hydrochloric acid (17.5 ml. of 11.4 N) to a solution of piperazine hexahydrate (38.8 g.) in ethanol (100 ml.). The solution was heated to 70° C., stirred vigorously and treated with *p*-methoxybenzyl chloride (15.7 g.) added dropwise over a period of 10 minutes. Stirring was continued at 70° C. for 1 hour after this addition was complete. After cooling and basification with sodium hydroxide as described in earlier examples the *product* was isolated by extraction with benzene followed by distillation at reduced pressure. It had b.p. 130° to 136° C. at 1.5 mm. The *dihydrochloride* had m.p. 260° C. (with decomposition).

EXAMPLE 15.

N-*p*-Chlorobenzyl piperazine

This derivative was prepared as described in the previous example but using *p*-chlorobenzyl chloride (16.1 g.) in place of *p*-methoxybenzyl chloride. The *product* had b.p. 132° to 134° C. at 1.4 mm.

EXAMPLE 16.

N[α-Naphthylmethyl]-piperazine

This derivative was prepared as described in Example 14 but using α-chloromethyl naphthalene (17.7 g.) in place of *p*-methoxybenzyl chloride. The *product* b.p. 180° to 184° C. at 1.5 mm. solidified and had m.p. 58° to 62° C.

EXAMPLE 17.

N[-6-(1:2:3:4-Tetrahydronaphthyl)-methyl]-piperazine

A solution of monopiperazinium chloride was prepared *in situ* as described in Example 14 and reacted with 6-chloromethyl-1:2:3:4-tetrahydronaphthalene (18.1 g.). Isolation in the normal manner furnished the *product* b.p. 172° to 176° C. at 1.5 mm.

EXAMPLE 18.

N-β-Phenethyl piperazine

A solution of monopiperazinium chloride, prepared *in situ* from piperazine hexahydrate (38.8 g.), concentrated hydrochloric acid (17.3 ml. of 11.55 N) and ethanol (160 ml.) was cooled to 20° C., stirred, and treated dropwise with β-phenethyl bromide (18.5 g.). The solution was stirred for 2 hours at 20° C. and for 30 minutes at 70° C. The *product* isolated in the normal manner, had b.p. 110° to 114° C. at 0.2 mm. The *dihydrochloride* had m.p. 280° to 282° C. (with decomposition).

EXAMPLE 19.

N-γ-Phenylpropyl piperazine

A solution of monopiperazinium chloride prepared *in situ* from piperazine hexahydrate (38.8 g.) and concentrated hydrochloric acid (17.4 ml. of 11.5 N) in β-ethoxyethanol, was stirred and treated at 30° C. with γ-phenylpropylbromide (20.0 g.) added dropwise. Stirring was continued for 15 minutes at 30° C. and for 2 hours at 70° C. After removal of β-ethoxyethanol at reduced pressure the *product*, isolated by standard procedure, had b.p. 122° to 128° C. at 0.5 mm.

EXAMPLE 20.

N-6-Phenylhexyl piperazine

This derivative was prepared by reaction of 6-phenylhexyl bromide with monopiperazinium chloride in β-ethoxyethanol for 5 hours at 70° to 80° C. The *product*, isolater normally, had b.p. 163° to 170° C. at 1.0 mm. and 143° C. at 0.3 mm.

EXAMPLE 21.

N-γ-*o*-Toloxypropyl piperazine

Reaction of 3-*o*-toloxypropyl bromide with monopiperazinium chloride in ethanol yielded the *product* as a viscous oil, b.p. 135° C. at 0.1 mm. The *dihydrochloride* had m.p. 233° C. after crystallisation from aqueous ethanol.

EXAMPLE 22.

N-γ-2:6-Xyloxypropyl piperazine

This derivative was obtained as an oil, b.p. 136° C. at 0.05 mm. by condensation of 2:6-

xyloxypropyl bromide with monopiperazinium chloride in ethanol in the usual manner.

EXAMPLE 23.

N-Methyl piperazine

To a solution of monopiperazinium chloride (2 moles) in ethanol (800 ml.) was added dimethyl sulphate (1 mole) dropwise with stirring over 20 minutes. Stirring was continued for 90 minutes and reaction completed by heating at 70° C. for 2 hours. After cooling, hydrochloric acid (1 mole) was added and precipitated piperazine *bis* salts filtered off after cooling.

The filtrate was concentrated and treated with a concentrated solution of sodium methoxide (3 moles) and the separated sodium salts were filtered off. Concentration of the filtrate followed by distillation at atmospheric pressure yielded the product, b.p. 136° C.

EXAMPLE 24.

N-Ethyl piperazine

To a stirred solution of monopiperazinium chloride (1 mole) in ethanol (400 ml.) was added ethyl bromide (0.55 mole) and the solution left for 1 hour at room temperature, reaction being completed by heating under reflux for 2 hours. Procedure was then as in the previous Example. The *product* had b.p. 156° to 158° C. at atmospheric pressure.

EXAMPLE 25.

1:3-bis-N-Piperazinopropane

Trimethylene dibromide (20.19 g.) was added with stirring at 35° C. to a solution of monopiperazinium chloride prepared from anhydrous piperazine (34.4 g.) and concentrated hydrochloric acid (34.4 ml. of 11.5 N) in ethanol (100 ml.). The solution was heated at 90° C. for 30 minutes, cooled, and concentrated hydrochloric acid (17.2 ml. of 11.5 N) added. It was then evaporated to dryness at reduced pressure, the residue boiled with ethanol (200 ml.) and filtered when cold to remove insoluble piperazine *bis* salts. The alcoholic filtrate was treated with a solution of sodium methoxide prepared from sodium (9.2 g.) in methanol (150 ml.). The precipitated sodium chloride was filtered off and the filtrate concentrated. The residual oil was distilled at 0.1 mm. to yield the *product* as an oil, b.p. 132° to 135° C. The product formed a *tetrapicrate* of m.p. 270° to 272° C. (with decomposition).

EXAMPLE 26.

1:2-bis-N-Piperazinoethane

This derivative was prepared as in the previous example using ethylene dibromide in place of trimethylene dibromide. The *product* had m.p. 97° to 99° C. after crystallisation from benzene and formed a *tetrapicrate* of m.p. 275° C. (with decomposition).

EXAMPLE 27.

1-(*p*-tert.-Butylbenzyl)-piperazine

p-tert.-Butylbenzyl bromide (22.7 g.) was added at 20° C. with stirring to a solution of *mono*piperazinium chloride (2 mole equivs.) prepared *in situ* by adding concentrated hydrochloric acid (17.3 ml. of 11.5 N) to piperazine hexahydrate (38.8 g.) in ethanol (80 ml.). After the addition was complete the mixture was stirred for 1 hour at room temperature and then for 30 minutes at 70° C. The *product*, isolated as described in earlier examples had b.p. 122 to 124° C. at 0.5 mm. and m.p. 50 to 54° C. The *dihydrochloride* crystallised from ethanol as a *hemihydrate*, m.p. 319 to 320° C. (with decomposition).

PREPARATION OF MONOPIPERAZINIUM CHLORIDE

Anhydrous piperazine (45.4 g., 0.53 mole) was dissolved in absolute ethanol (300 ml.) and a solution of hydrogen chloride (19.35 g., 0.53 mole) in absolute ethanol was added with stirring keeping the temperature between 15 and 20° C. After addition the mixture was stirred for 20 minutes at room temperature and the hydrochloride was filtered off. The *product* was slightly hygroscopic. After recrystallisation from absolute ethanol it had m.p. 172 to 174° C.

PREPARATION OF MONOPIPERAZINIUM BROMIDE

Anhydrous piperazine (8.6 g., 0.1 mole) was dissolved in ethanol (20 ml.) and 47% hydrobromic acid (17.2 g., 0.1 mole) was added. The solution was stripped to dryness and the solids recrystallised twice from aqueous alcohol to yield faint yellow, irregular prisms m.p. 210 to 212° C.

WHAT WE CLAIM IS:—

1. A process for the manufacture of an N-mono-substituted piperazine which process comprises reacting in the presence of an organic or aqueous organic solvent an alkylating agent containing up to 6 carbon atoms or an aralkylating agent with a monopiperazinium salt derived from an acid with dissociation constant lying below the second acid dissociation constant of the piperazine in the solvent system employed for the condensation.

2. A process as claimed in claim 1 wherein the alkylating agent is methyl or ethyl sulphate.

3. A process as claimed in claim 1 wherein the alkylating agent is an alkyl bromide or iodide.

4. A process as claimed in claim 1 wherein the aralkylating agent is a chloride, bromide or iodide of the type

$$Hal.(CH_2)_nAr,$$

where n is not greater than 6 and Ar is an aromatic nucleus.

5. A process as claimed in claim 1 wherein the alkylating agent is an α,ω-dibromide or diiodide containing up to 6 carbon atoms.

6. A process as claimed in any one of the preceding claims wherein the monopiper-

azinium salt is prepared by reacting piperazine or its hexahydrate in an organic or aqueous organic solvent with the appropriate quantity of acid.

7. A process as claimed in claim 6 wherein the monopiperazinium salt is employed *in situ* without prior isolation, the amount of acid being added being as nearly as possible the quantity necessary to convert the piperazine to the mono-piperazinium salt.

8. A process as claimed in claim 7 wherein the monopiperazinium salt is monopiperazinium chloride or bromide.

9. A process for the manufacture of an N-mono-substituted piperazine substantially as described with reference to any one of the specific examples hereinbefore set forth.

A. G. R. CLARKE,
Agent for the Applicants.

PROVISIONAL SPECIFICATION

Improvements in or relating to the Manufacture of N-Mono-Substituted Piperazines

We, THE BRITISH DRUG HOUSES LIMITED, a British Company, of 16—34, Graham Street, City Road, London, N.1, do hereby declare this invention to be described in the following statement:—

This invention is for improvements in or relating to organic compounds and has particular reference to a new process for the manufacture of N-monosubstituted piperazines.

It is an object of the present invention to provide a new process for the manufacture of a wide range of N-monosubstituted piperazines as hereinafter defined, which process gives yields which are often substantially higher than those obtained by the employment of methods hitherto known to those skilled in the art.

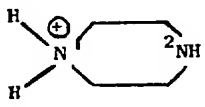
N-Monosubstituted piperazines are essential intermediates in the manufacture of piperazine derivatives employed in medicine for example as antihistaminics, travel-sickness remedies and anthelmintics.

The manufacture of the N-monosubstituted derivatives of piperazine is complicated by the fact that there are present in piperazine having the formula

(I)

two basic centres N^1 and N^2 of equal reactivity towards alkylating agents, so that monoalkylation without simultaneous dialkylation is difficult to achieve. Thus monoalkylation of piperazine by methods hitherto known to those skilled in the art generally gives mixtures containing the unchanged base, the N^1-monosubstituted derivative and significant quantities of the N^1N^2-disubstituted derivative, which mixtures are generally difficult to separate so that there is considerable loss in yield of N^1-monosubstituted derivative. In addition the unwanted production of significant quantities of the N^1N^2-disubstituted derivative is wasteful.

We have made the discovery that, in contrast to piperazine itself, the two reactive centres N^1 and N^2 present in the monopiperazinium ion (II)



(II)

derived from the corresponding monopiperazinium salt (III)

(III)

where R is an anionic radical derived from an acid as hereinafter defined, are no longer equal in reactivity towards alkylating agents, and that alkylation of salts containing such monopiperazinium ions gives excellent yields of N-monosubstituted piperazines substantially free from N^1N^2-disubstituted derivatives. This is a discovery of industrial importance as it opens the way to the economic production of a wide range of N-monosubstituted derivatives of piperazine in excellent yields and by a substantially one-stage process.

According to the present invention there is provided a process for the manufacture of an N-monosubstituted piperazine which process comprises reacting a monopiperazinium salt with an alkylating agent containing up to 6 carbon atoms or aralkylating agent in the presence of an organic or aqueous organic solvent.

The monopiperazinium salt is prepared by reacting piperazine or its hexahydrate in an organic or aqueous organic solvent with the appropriate quantity of acid. The monopiperazinium salt will separate from solution or remain in the solution from which it may be recovered by removal of the solvent. It is, however, convenient to employ the mono-

piperazinium salts *in situ* without prior isolation, the amount of acid added being as nearly as possible the quantity necessary to convert the piperazine to the monopiperazinium salt.

The alkylating agent may be methyl or ethyl sulphate or an alkyl halide, in particular an alkyl bromide or iodide, but not an alkyl fluoride.

The alkylating or aralkylating agent may have two reactive centres; thus it may be an aliphatic or araliphatic $\alpha.\omega$-dichloride, dibromide or diiodide, in particular the alkylating agent may be an $\alpha.\omega$-dibromide or diiodide containing up to 6 carbon atoms.

The aralkylating agent may be a chloride, bromide or iodide of the type

$$Hal.(CH_2)_nAr,$$

where n is not greater than 6 and Ar is an aromatic nucleus and in particular a phenyl, naphthyl or diphenyl nucleus, which may be additionally substituted by alkyl, alkoxy, halogen or nitro groups.

The invention may be applied to monopiperazinium salts derived from acids as hereinafter defined providing the corresponding monopiperazinium salts are soluble in the solvents employed for the condensations at the temperatures at which the condensations are performed, do not react with the solvents employed for the condensations, and do not decompose under the experimental conditions employed for the condensations.

The invention may be applied to monopiperazinium salts derived from acids with dissociation constants lying below the second acid dissociation constant of the piperazine in the solvent system employed for the condensation. Thus when piperazine is employed in aqueous ethanolic solution the monopiperazinium salt may be derived from acids with dissociation constants lying below the second acid dissociation constant of piperazine (pKa_2 =9.66 in water at 25° C.). Acids which satisfy this condition and thus fall within the scope of the invention are exemplified by:

acetic acid,
succinic acid,
citric acid,
benzoic acid,
toluene *p*-sulphonic acid,
hydrochloric and hydrobromic acids, and
sulphuric acid.

Hydrochloric acid is the preferred acid.

The invention may be performed in a variety of solvent systems including such organic solvents as dioxan, ethoxyethanol and alkanols containing up to 5 carbon atoms, with or without the addition of water. Aqueous ethanol is the preferred solvent system.

The invention may be performed by adding the appropriate proportion of alkylating or aralkylating agent to a solution of the monopiperazinium salt in the appropriate solvent. Heating the mixture may be necessary with alkylating agents of low reactivity.

In carrying out the process of the invention economically, it is clearly necessary to adjust the relative proportions of alkylating or aralkylating agent and monopiperazinium salt in such a way as to obtain as high yield of product as possible without employment of too great an excess of monopiperazinium salt. It will be obvious to those skilled in the art that the proportion of monopiperazinium salt employed should not be less than one molar proportion relative to each alkylating unit. At the same time it is economically inadvisable to employ substantially more than 2.1 molar proportions of monopiperazinium salt to each alkylating unit. With monopiperazinium salts derived from hydrochloric acid and other strong mineral acids, yields of monosubstitution product approaching the optimum yield are obtained by employing 2.0 to 2.1 molar proportions of monopiperazinium salt to each alkylating unit. With weak organic acids it is possible to use a smaller proportion of monopiperazinium salt with only moderate drop in yield of N-monosubstitution product, but the proportion of monopiperazinium salt employed should not be less than one molar proportion to each alkylating unit otherwise the process becomes uneconomical.

Following is a description by way of example of methods of carrying the invention into effect.

EXAMPLE 1.

N-*m*-Methylbenzylpiperazine

A solution of monopiperazinium chloride (24.5 g., 0.2 mole) in a mixture of ethanol (100 ml.) and water (35 ml.) was cooled to 20° C. and *m* - methylbenzylbromide (18.5 gm., 0.1 mole) added with stirring. Stirring was continued for one hour at 20° C. and then for 30 minutes at 70° C., when the ethanol was removed at reduced pressure. The residue was made basic by the addition of a slight excess of 5N sodium hydroxide. The oil which separated was removed and the aqueous layer extracted with benzene. The benzene extract was combined with the oil and the benzene distilled off. Distillation of the residue at 0.2 mm. yielded N-*m*-methylbenzylpiperazine as an oil, b.p. 100° to 105° C.

EXAMPLE 2.

A solution of monopiperazinium chloride was prepared *in situ* in aqueous methyl alcohol by adding hydrochloric acid (17.5 ml. of 11.4N, 0.2 mole) to a solution of piperazine hexahydrate (38.8 g., 0.2 mole) in methanol (100 ml.). The solution was cooled to 20° C. and *m*-methylbenzylbromide (18.5

gm., 0.1 mole) added with stirring. Stirring was continued for 30 minutes at 70° C. N-*m*-Methylbenzylpiperazine was isolated exactly as described in Example 1, as an oil, b.p. 123° to 127° C. at 1.5 mm.

EXAMPLE 3.

The reaction described in Example 2 was carried out in exactly the same way except that *iso*propanol (100 ml.) was used in place of methanol. The N-*m*-methylbenzylpiperazine was obtained as an oil, b.p. 122° to 126° C. at 1.5 mm.

EXAMPLE 4.

The reaction carried out in Example 2 was repeated using β-ethoxyethanol (100 ml.) in place of methanol. The mixture was stirred vigorously throughout because of the tendency to form two layers. The N-*m*-methylbenzylpiperazine isolated in the normal manner, had b.p. 122° to 124° C. at 1.5 mm.

EXAMPLE 5.

A solution of monopiperazinium bromide was prepared *in situ* in aqueous ethanol by adding 47% hydrobromic acid (34.5 g., 0.2 mole) to a solution of piperazine hexahydrate (38.8 g., 0.2 mole) in ethanol (80 ml.). The solution was heated to 70° C. and *m*-methylbenzylbromide (18.5 g., 0.1 mole) added slowly. Stirring was continued at 70° C. for 30 minutes. Isolation of the N-*m*-methylbenzylpiperazine as described in Example 1 yielded an oil, b.p. 100° to 102° C. at 0.2 mm.

EXAMPLE 6.

A solution of monopiperazinium acetate was prepared *in situ* in aqueous ethanol by adding glacial acetic acid (6.0 g., 0.1 mole) to a solution of piperazine hexahydrate (19.4 gm., 0.1 mole) in a mixture of ethanol (100 ml.) and water (20 ml.). The solution was heated to 70° C. and *m*-methylbenzylbromide (18.5 g., 0.1 mole) added slowly with stirring. Stirring was continued at 70° C. for 30 minutes. N-*m*-Methylbenzylpiperazine, isolated in the manner described in previous examples, had b.p. 123° to 125° C., at 1.5 mm.

EXAMPLE 7.

A suspension of monopiperazinium sulphate was prepared *in situ* in aqueous ethanol by adding 98% sulphuric acid (5.3 ml. of 37.5 N, 0.1 mole) to a solution of piperazine hexahydrate (38.8 g., 0.2 mole) in a mixture of ethanol (100 ml.) and water (15 ml.). By heating to 70° C. a solution was formed; m-methylbenzylbromide (18.5 g., 0.1 mole) was then added slowly and the stirring continued at 70° C. for 30 minutes. The N-m-methylbenzylpiperazine was isolated exactly as described in Example 1, as an oil, b.p. 103° to 105° C. at 0.2 mm.

EXAMPLE 8.

N-Methylpiperazine

A solution of monopiperaziniumchloride in aqueous ethanol was prepared *in situ* by adding slowly concentrated hydrochloric acid (173 ml., 2 moles) to a solution of piperazine hexahydrate (388 g., 2 moles) in ethanol (800 ml.) in a 3-neck round-bottomed flask fitted with stirrer, condenser and dropping-funnel. The mixture was cooled to room temperature, stirred and methyl iodide (142 g., 1 mole) added slowly. After the addition was complete, stirring was continued for 90 minutes at room temperature and then for 2 hours at 70° C. The mixture was cooled, treated with concentrated hydrochloric acid (86.5 ml. of 11.6 N, (1 mole), concentrated to half bulk and the insoluble piperazine *bis* hydrochloride filtered off. The filtrate was evaporated to dryness at reduced pressure, dissolved in methanol (1 litre) and filtered to remove a little more of the insoluble piperazine *bis* hydrochloride. The filtrate was treated with a concentrated solution of sodium methoxide (108 g., 2 mole), filtered to remove sodium chloride and distilled through an efficient fractionating column. After removal of methanol and a small fore-run, N-methylpiperazine was obtained, b.p. 134° to 136° C.

EXAMPLE 9.

N-*n*-Amylpiperazine

A solution of monopiperazinium chloride was prepared *in situ* in aqueous ethanol by adding concentrated hydrochloric acid (17.5 ml. of 11.4 N, 0.2 mole) to a stirred solution of piperazine hexahydrate (38.8 gm.) in ethanol (180 ml.). The mixture was cooled to 20° C. and *n*-amylbromide (15.1 g., 0.1 mole) added slowly. After the addition was completed, stirring was continued for 1 hour at room temperature and for 30 minutes at 70° C. The N-*n*-amylpiperazine, isolated in the normal manner, had b.p. 110° to 114° C. at about 30 mm.

EXAMPLE 10.

N-*o*-Methylbenzylpiperazine

A solution of monopiperazinium chloride was prepared *in situ* in aqueous ethanol by adding concentrated hydrochloric acid (17.3 ml. of 11.5 N, 0.2 mole) to a stirred solution of piperazine hexahydrate (38.8 gm., 0.2 mole) in ethanol (80 ml.). The mixture was cooled to 20° C. and *o*-methylbenzylbromide (18.5 gm., 0.1 mole) added slowly dropwise. After the addition was complete, the mixture was stirred for 2 hours at room temperature and for 30 minutes at 70° C. The N-*o*-methylbenzylpiperazine, isolated as described in earlier examples, had b.p. 104° to 106° C. at 0.05 mm.

EXAMPLE 11.

N-*m*-Methylbenzyl piperazine

A solution of monopiperazinium toluene *p*-sulphonate was prepared *in situ* from piperazine hexahydrate (38.8 g.) and toluene *p*-sulphonic acid monohydrate (38 g.) in ethanol (80 ml.). The solution was cooled to 20° C. and *m*-methylbenzyl bromide (18.5 g.) added

with stirring. Stirring was continued for 1 hour at room temperature and for 30 minutes at 70° C. The *product* isolated as described in Example 1 had b.p. 130° to 132° C. at 1.4 mm.

EXAMPLE 12.

A solution of monopiperazinium benzoate was prepared *in situ* from piperazine hexahydrate (38.8 g.) and benzoic acid (24.4 g.) in ethanol (80 ml.). This solution was reacted with m-methylbenzyl bromide (18.5 g.) exactly as described in Example 11. The *product*, isolated as above had b.p. 110° to 116° C. at 0.6 mm.

EXAMPLE 13.

A solution of monopiperazinium citrate was prepared *in situ* by dissolving piperazine hexahydrate (29.1 g.) and citric acid monohydrate (10.5 g.) in ethanol (60 ml.), and reacted as described in previous examples with *m*-methylbenzyl bromide (18.5 g.). The *product* isolated in the usual manner, had b.p. 110° to 114° C. at 0.5 mm.

EXAMPLE 14.

N-*p*-Methoxybenzyl piperazine

A solution of monopiperazinium chloride was prepared *in situ* by adding concentrated hydrochloric acid (17.5 ml. of 11.4 N) to a solution of piperazine hexahydrate (38.8 g.) in ethanol (100 ml.). The solution was heated to 70° C., stirred vigorously and treated with *p*-methoxybenzyl chloride (15.7 g.) added dropwise over a period of 10 minutes. Stirring was continued at 70° C. for 1 hour after this addition was complete. After cooling and basification with sodium hydroxide as described in earlier examples the *product* was isolated by extraction with benzene followed by distillation at reduced pressure. It had b.p. 130° to 136° C. at 1.5 mm. The *dihydrochloride* had b.p. 260° C. (with decomposition).

EXAMPLE 15.

N-*p*-Chlorobenzyl piperazine

This derivative was prepared as described in the previous example but using *p*-chlorobenzyl chloride (16.1 g.) in place of *p*-methoxybenzyl chloride. The *product* had b.p. 132° to 134° C. at 1.4 mm.

EXAMPLE 16.

N-[α-Naphthylmethyl]-piperazine

This derivative was prepared as described in Example 14 but using α-chloromethyl naphthalene (17.7 g.) in place of *p*-methoxybenzyl chloride. The *product* b.p. 180° to 184° C. at 1.5 mm. solidified and had m.p. 58° to 62° C.

EXAMPLE 17.

N-[6-(1:2:3:4-Tetrahydronaphthyl)-methyl]-piperazine

A solution of monopiperazinium chloride was prepared *in situ* as described in Example 14 and reacted with 6-chloromethyl-1:2:3:4-tetrahydronaphthalene (18.1 g.). Isolation in the normal manner furnished the *product* b.p. 172° to 176° C. at 1.5 mm.

EXAMPLE 18.

N-β-Phenethyl piperazine

A solution of monopiperazinium chloride, prepared *in situ* from piperazine hexahydrate (38.8 g.), concentrated hydrochloric acid (17.3 ml. of 11.55 N) and ethanol (160 ml.) was cooled to 20° C., stirred, and treated dropwise with β-phenethyl bromide (18.5 g.). The solution was stirred for 2 hours at 20° C. and for 30 minutes at 70° C. The *product* isolated in the normal manner, had b.p. 110° to 114° C. at 0.2 mm. The *dihydrochloride* had m.p. 280° to 282° C. (with decomposition).

EXAMPLE 19.

N-γ-Phenylpropyl piperazine

A solution of monopiperazinium chloride prepared *in situ* from piperazine hexahydrate (38.8 g.) and concentrated hydrochloric acid (17.4 ml. of 11.5N) in β-ethoxyethanol, was stirred and treated at 30° C. with γ-phenylpropylbromide (20.0 g.) added dropwise. Stirring was continued for 15 minutes at 30° C. and for 2 hours at 70° C. After removal of β-ethoxyethanol at reduced pressure the *product*, isolated by standard procedure, had b.p. 122° to 128° C. at 0.5 mm.

EXAMPLE 20

N-6-Phenylhexyl piperazine

This derivative was prepared by reaction of 6-phenylhexyl bromide with monopiperazinium chloride in β-ethoxyethanol for 5 hours at 70° to 80° C. The *product*, isolated normally, had b.p. 163° to 170° C. at 1.0 mm. and 143° C. at 0.3 mm.

EXAMPLE 21.

N-γ-*o*-Toloxypropyl piperazine

Reaction of 3-*o*-toloxypropyl bromide with monopiperazinium chloride in ethanol yielded the *product* as a viscous oil, b.p. 135° C. at 0.1 mm. The *dihydrochloride* had m.p. 233° C. after crystallisation from aqueous ethanol.

EXAMPLE 22.

N-γ-2:6-Xyloxypropyl piperazine

This derivative was obtained as an oil, b.p. 136° C. at 0.05 mm. by condensation of 2:6-xyloxypropyl bromide with monopiperazinium chloride in ethanol in the usual manner.

EXAMPLE 23.

N-Methyl piperazine

To a solution of monopiperazinium chloride (2 moles) in ethanol (800 ml.) was added dimethyl sulphate (1 mole) dropwise with stirring over 20 minutes. Stirring was continued for 90 minutes and reaction completed by heating at 70° C. for 2 hours. After cooling, hydrochloric acid (1 mole) was added and precipitated piperazine *bis* salts filtered off after cooling.

The filtrate was concentrated and treated with a concentrated solution of sodium methoxide (3 moles) and the separated sodium salts were filtered off. Concentration of the filtrate followed by distillation at atmospheric

pressure yielded the product, b.p. 136° C.

EXAMPLE 24.

N-Ethyl piperazine

To a stirred solution of monopiperazinium chloride (1 mole) in ethanol (400 ml.) was added ethyl bromide (0.55 mole) and the solution left for 1 hour at room temperature, reaction being completed by heating under reflux for 2 hours. Procedure was then as in the previous example. The *product* had b.p. 156° to 158° C. at atmospheric pressure.

EXAMPLE 25

1:3-bis-N-Piperazinopropane

Trimethylene dibromide (20.19 g.) was added with stirring at 35° C. to a solution of monopiperazinium chloride prepared from anhydrous piperazine (34.4 g.) and concentrated hydrochloric acid (34.4 ml. of 11.5 N) in ethanol (100 ml.). The solution was heated at 90° C. for 30 minutes, cooled, and concentrated hydrochloric acid (17.2 ml. of 11.5 N) added. It was then evaporated to dryness at reduced pressure, the residue boiled with ethanol (200 ml.) and filtered when cold to remove insoluble piperazine *bis* salts. The alcoholic filtrate was treated with a solution of sodium methoxide prepared from sodium (9.2 g.) in methanol (150 ml.). The precipitated sodium chloride was filtered off and the filtrate concentrated. The residual oil was distilled at 0.1 mm. to yield the *product* as an oil, b.p. 132° to 135° C. The product formed a *tetrapicrate* of m.p. 270° to 272° C. (with decomposition).

EXAMPLE 26.

1:2-bis-N-Piperazinoethane

This derivative was prepared as in the previous example using ethylene dibromide in place of trimethylene dibromide. The *product* had m.p. 97° to 99° C. after crystallisation from benzene and formed a *tetrapicrate* of m.p. 275° C. (with decomposition).

A. G. R. CLARKE,
Agent for the Applicants.

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